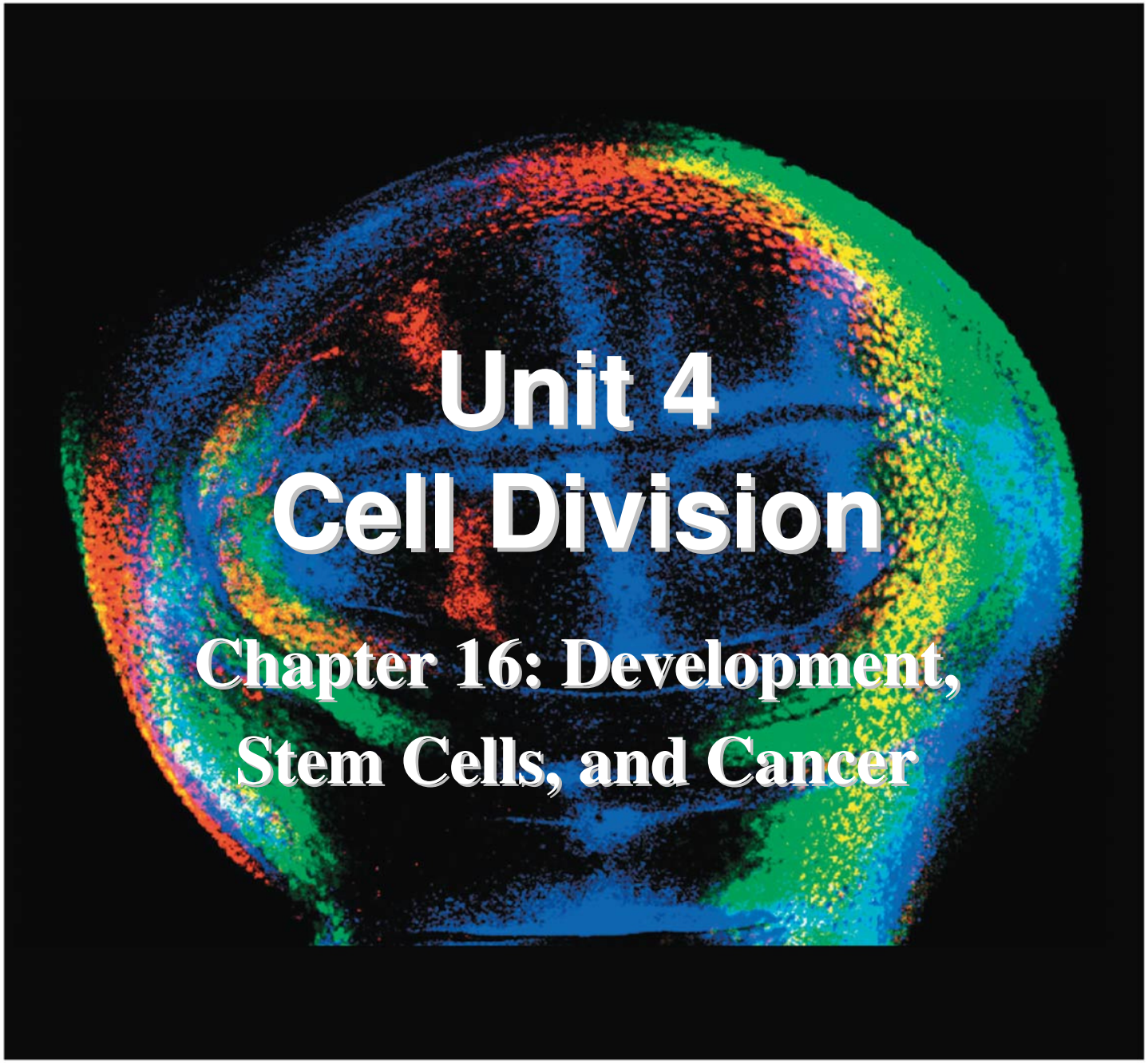


Unit 4
Cell Division

Chapter 16: Development, Stem Cells, and Cancer

Overview: Orchestrating Life's Processes

- The development of a fertilized egg into an adult requires a precisely regulated program of gene expression
- Understanding this program has progressed mainly by studying **model organisms**
  - Ex: Fruit flies
- Stem cells are key to the developmental process
- Orchestrating proper gene expression by all cells is crucial for life

Concept 16.1: A program of differential gene expression leads to the different cell types in a multicellular organism

- A fertilized egg gives rise to many different cell types
- Cell types are organized successively into tissues, organs, organ systems, and the whole organism
- Gene expression orchestrates the developmental programs of animals

- The transformation from zygote to adult results from
  - Cleavage (cell division)
  - Cell differentiation
  - Pattern formation
  - Morphogenesis
  - Cell growth
  - Cell death (apoptosis)

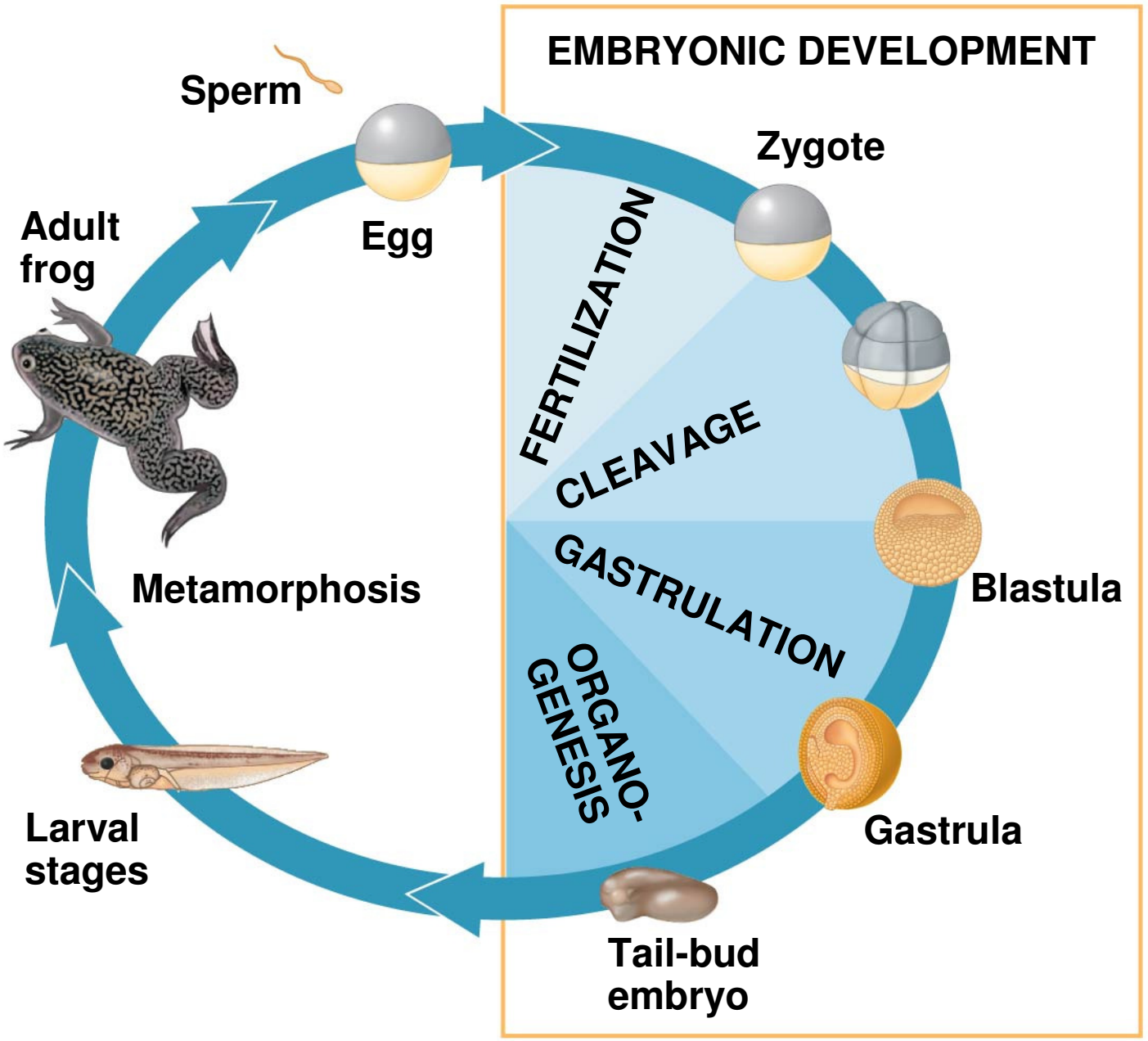
(a) Fertilized eggs of a frog

(b) Newly hatched tadpole

Concept 36.4: Fertilization, cleavage, and gastrulation initiate embryonic development

- Across animal species, embryonic development involves common stages occurring in a set order
- First is fertilization, which forms a zygote
- During the cleavage stage, a series of mitoses divide the zygote into a many-celled embryo
- The resulting blastula then undergoes rearrangements into a three-layered embryo called a gastrula

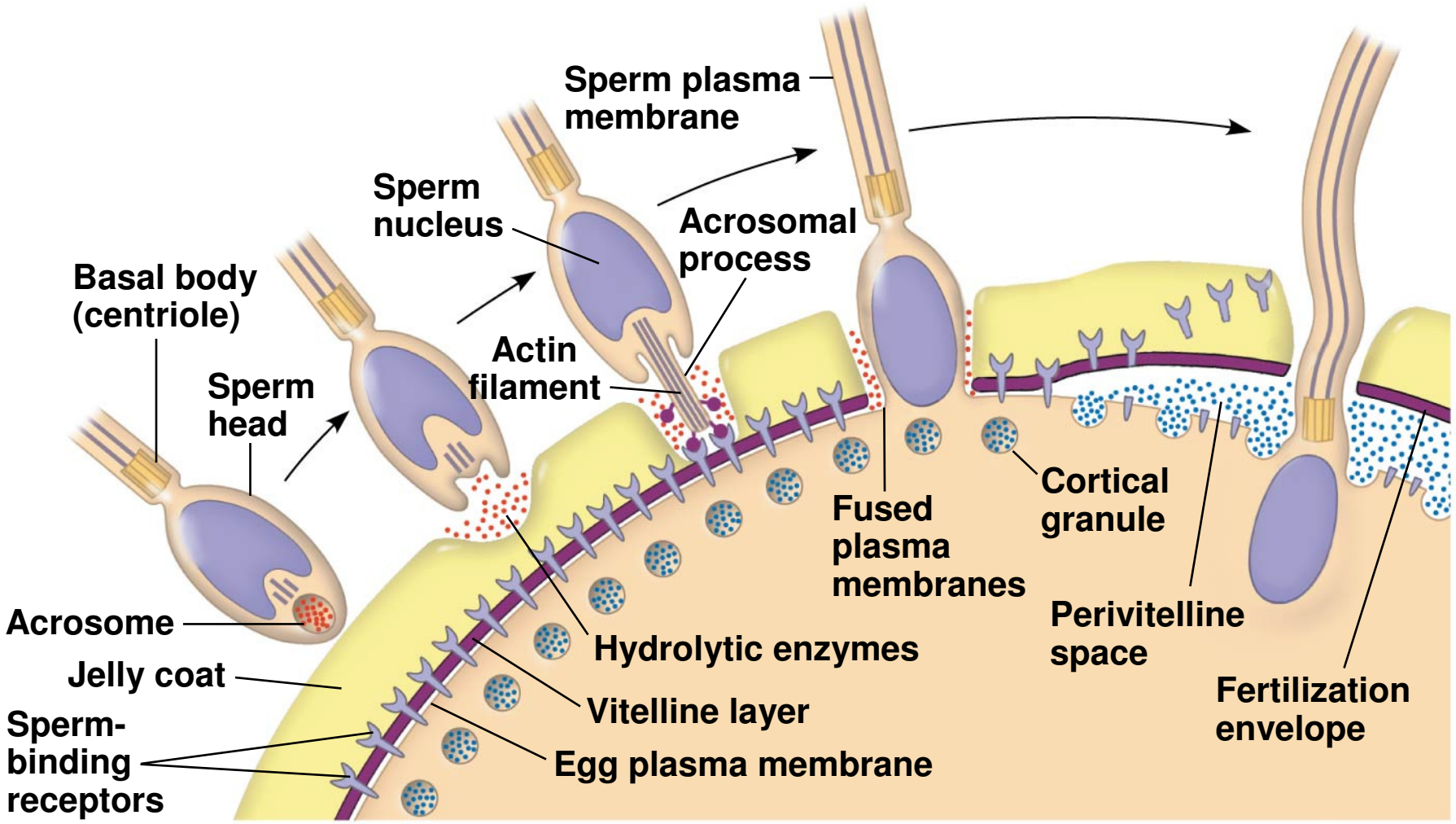
Figure 36.14


EMBRYONIC DEVELOPMENT
Sperm
Egg
Zygote
FERTILIZATION
CLEAVAGE
GASTRULATION
ORGANO-
GENESIS
Blastula
Gastrula
Tail-bud
embryo
Larval
stages
Metamorphosis
Adult
frog

Fertilization

- Molecules and events at the egg surface play a crucial role in each step of fertilization
  - Sperm penetrate the protective layer around the egg
  - Receptors on the egg surface bind to molecules on the sperm surface
  - Changes at the egg surface prevent **polyspermy**
    - The entry of multiple sperm nuclei into the egg
    - Otherwise there could be an abnormal number of chromosomes

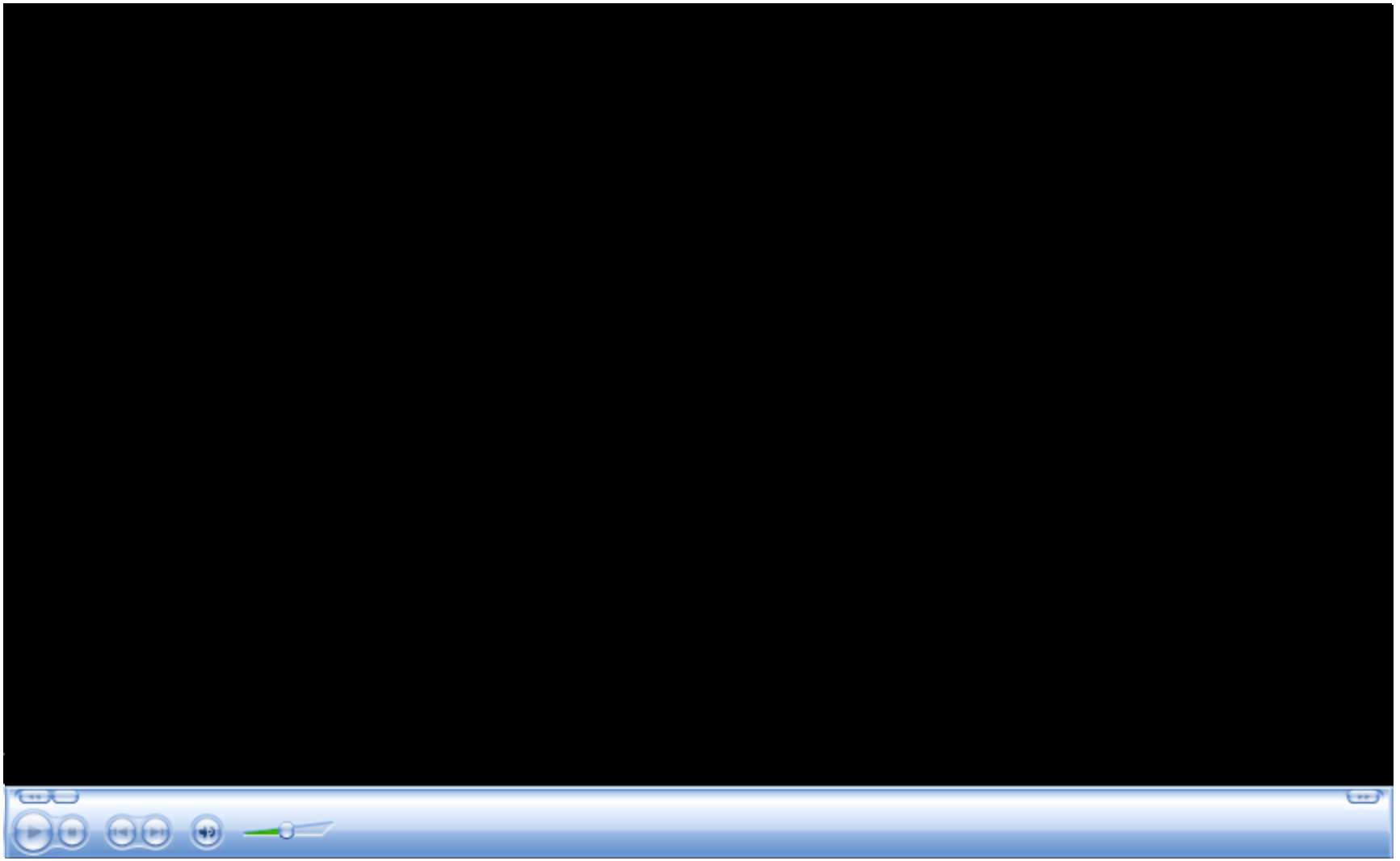
Figure 35.15-5



- Major function of fertilization is to combine haploid sets of chromosomes from 2 individuals into a single diploid cell, the zygote
- The events of fertilization also initiate metabolic reactions that trigger the onset of embryonic development, thus “activating” the egg
  - Leads to events such as increased protein synthesis that precede the formation of a diploid nucleus
- Sperm entry triggers a release of Ca^{2+}, which activates the egg and triggers the cortical reaction
  - The slow block to polyspermy

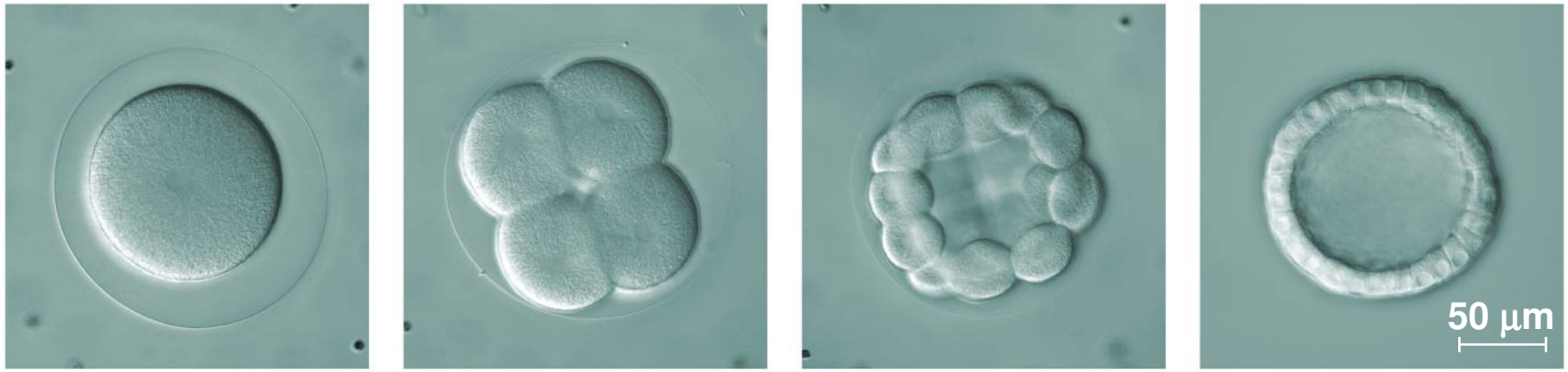
Cleavage and Gastrulation

- Fertilization is followed by **cleavage**
  - A period of rapid cell division without growth
  - Partitions the cytoplasm of one large cell into many smaller cells
- The **blastula** is a ball of cells with a fluid-filled cavity called a **blastocoel**
  - Produced after about five to seven cleavage divisions



Video: Cleavage of Egg

Figure 36.17



(a) Fertilized egg (b) Four-cell stage (c) Early blastula (d) Later blastula

- After cleavage, the rate of cell division slows
- The remaining stages of embryonic development are responsible for **morphogenesis**
  - Cellular and tissue-based processes by which the animal body takes shape

- During **gastrulation**, a set of cells at or near the surface of the blastula moves to an interior location, cell layers are established, and a primitive digestive tube forms
- The hollow blastula is reorganized into a two- or three-layered embryo called a **gastrula**
- The cell layers produced by gastrulation are called germ layers
  - The **ectoderm** forms the outer layer
  - The **endoderm** forms the inner layer
  - In vertebrates and other animals with bilateral symmetry, a third germ layer, the **mesoderm**, forms between the endoderm and ectoderm

Figure 36.18a-4

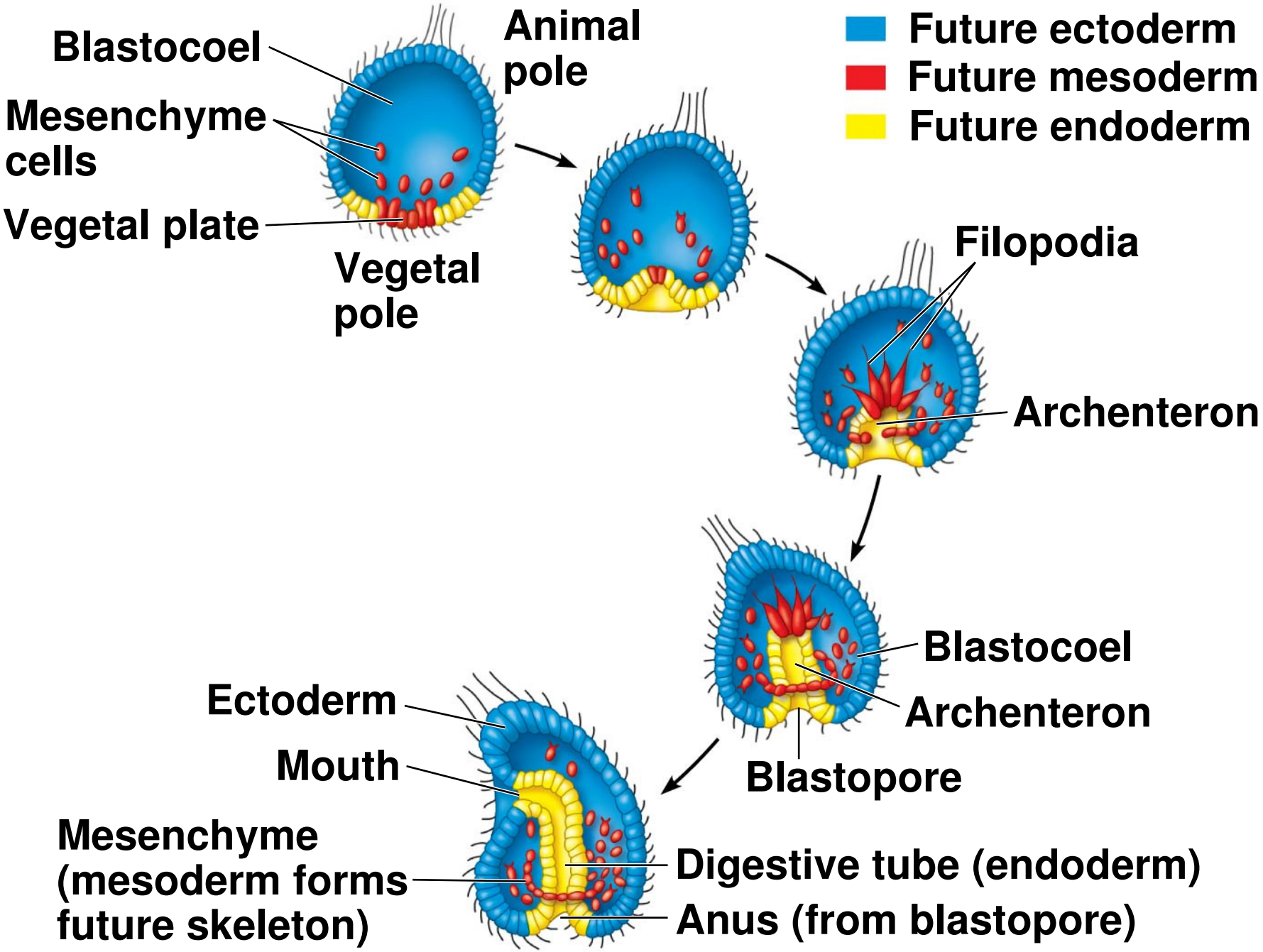
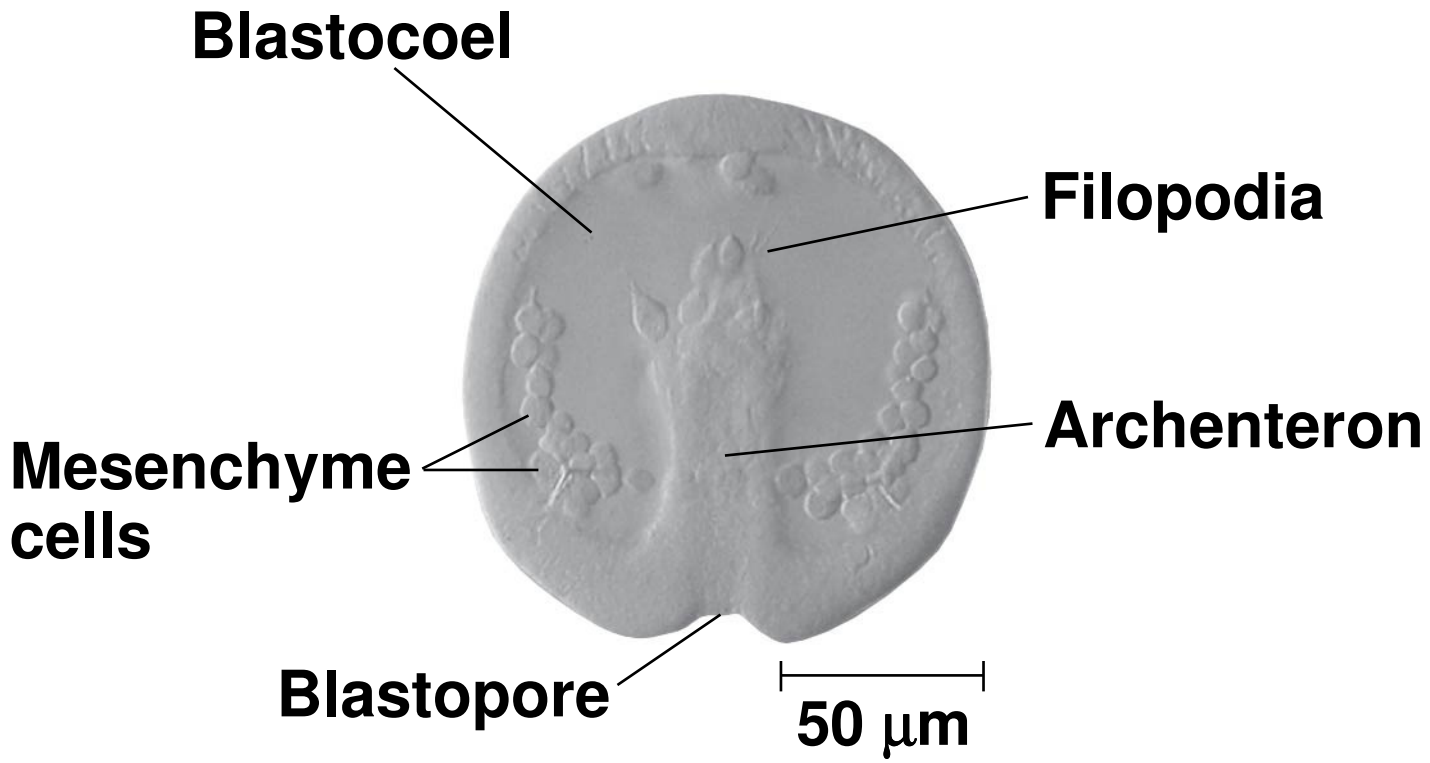


Figure 36.18b



- Cell movements and interactions that form the germ layers vary among species
- One distinction is whether the mouth develops from the first or second opening that forms in the embryo
  - *Protostomes*-mouth first
  - *Deuterostomes*-anus first, mouth second
    - Sea urchins and other echinoderms
    - Chordates (including humans!)

- Each germ layer contributes to a distinct set of structures in the adult animal
- Some organs and many organ systems derive from more than one germ layer

Figure 36.19

ECTODERM (outer layer of embryo)

- Epidermis of skin and its derivatives (including sweat glands, hair follicles)
- Nervous and sensory systems
- Pituitary gland, adrenal medulla
- Jaws and teeth
- Germ cells

MESODERM (middle layer of embryo)

- Skeletal and muscular systems
- Circulatory and lymphatic systems
- Excretory and reproductive systems (except germ cells)
- Dermis of skin
- Adrenal cortex

ENDODERM (inner layer of embryo)

- Epithelial lining of digestive tract and associated organs (liver, pancreas)
- Epithelial lining of respiratory, excretory, and reproductive tracts and ducts
- Thymus, thyroid, and parathyroid glands

A Genetic Program for Embryonic Development (Ch 16.1 Continued)

- Cell **differentiation** is the process by which cells become specialized in structure and function
- The physical processes that give an organism its shape constitute **morphogenesis**
- Activities of a cell depend on the genes it expresses and the proteins it produces
  - Cells in an organism have the same genome
  - So differential gene expression results from genes being regulated differently in each cell type

Cytoplasmic Determinants and Inductive Signals

- One important source of information early in development is the egg's cytoplasm
  - Contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg
- **Cytoplasmic determinants** are maternal substances in the egg that influence early development
  - As the zygote divides by mitosis, the resulting cells contain different cytoplasmic determinants
    - This leads to different gene expression

- The other major source of developmental information is the environment around the cell, especially signals from nearby embryonic cells
- In the process called **induction**, signal molecules from embryonic cells cause transcriptional changes in nearby target cells
- Thus, interactions between cells induce differentiation of specialized cell types!

Sequential Regulation of Gene Expression During Cellular Differentiation

- **Determination** commits a cell irreversibly to its final fate
  - Once a cell has undergone determination, an embryonic cell is irreversible committed to its final fate
- Determination precedes differentiation

Differentiation of Cell Types

- The outcome of determination, observable cell differentiation, is marked by the expression of genes for *tissue-specific proteins*
- The first evidence of differentiation is the production of mRNAs for these proteins
- Eventually, differentiation is observed as changes in cellular structure
- Transcription remains the principal regulatory point for maintaining appropriate gene expression
- Some “master regulatory genes” have been identified

Apoptosis: A Type of Programmed Cell Death

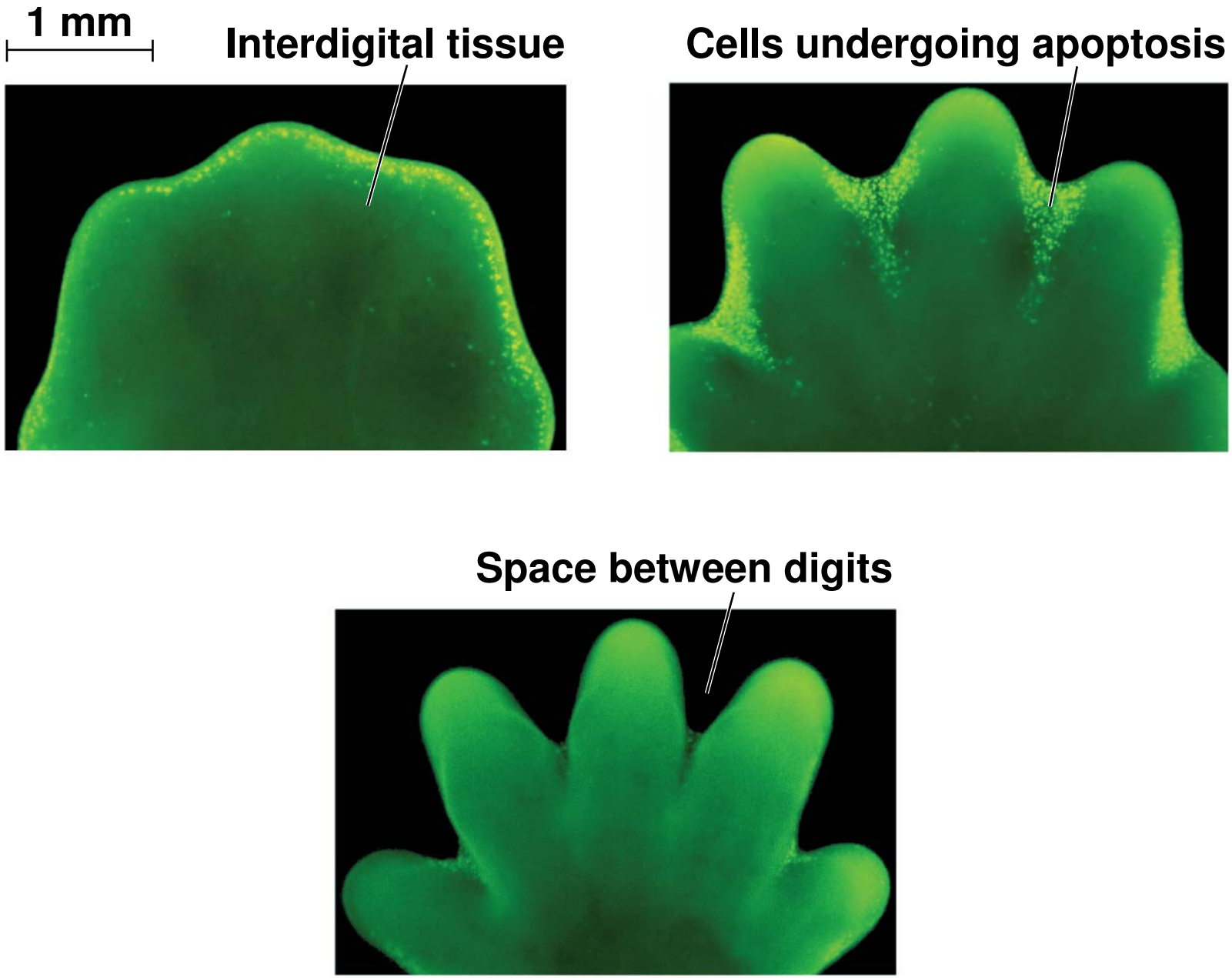
- While most cells are differentiating in a developing organism, some are genetically programmed to die
- **Apoptosis** is the best-understood type of "programmed cell death"
- Apoptosis also occurs in the mature organism in cells that are infected, damaged, or at the end of their functional lives

- During apoptosis, DNA is broken up and organelles and other cytoplasmic components are fragmented
- The cell becomes multilobed and its contents are packaged up in vesicles
- These vesicles are then engulfed by scavenger cells
- Apoptosis protects neighboring cells from damage by nearby dying cells

- Apoptosis is essential to development and maintenance in all animals
- It is known to occur also in fungi and yeasts
- In vertebrates, apoptosis is essential for normal nervous system development and morphogenesis of hands and feet (or paws)

- An organism's body plan (3-D arrangement) must be established and superimposed on the differentiation process

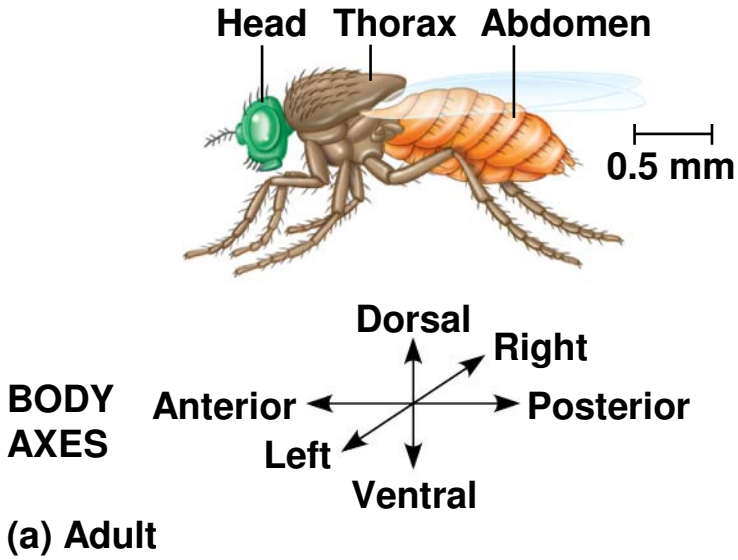
Figure 16.6


1 mm
Interdigital tissue
Cells undergoing apoptosis
Space between digits

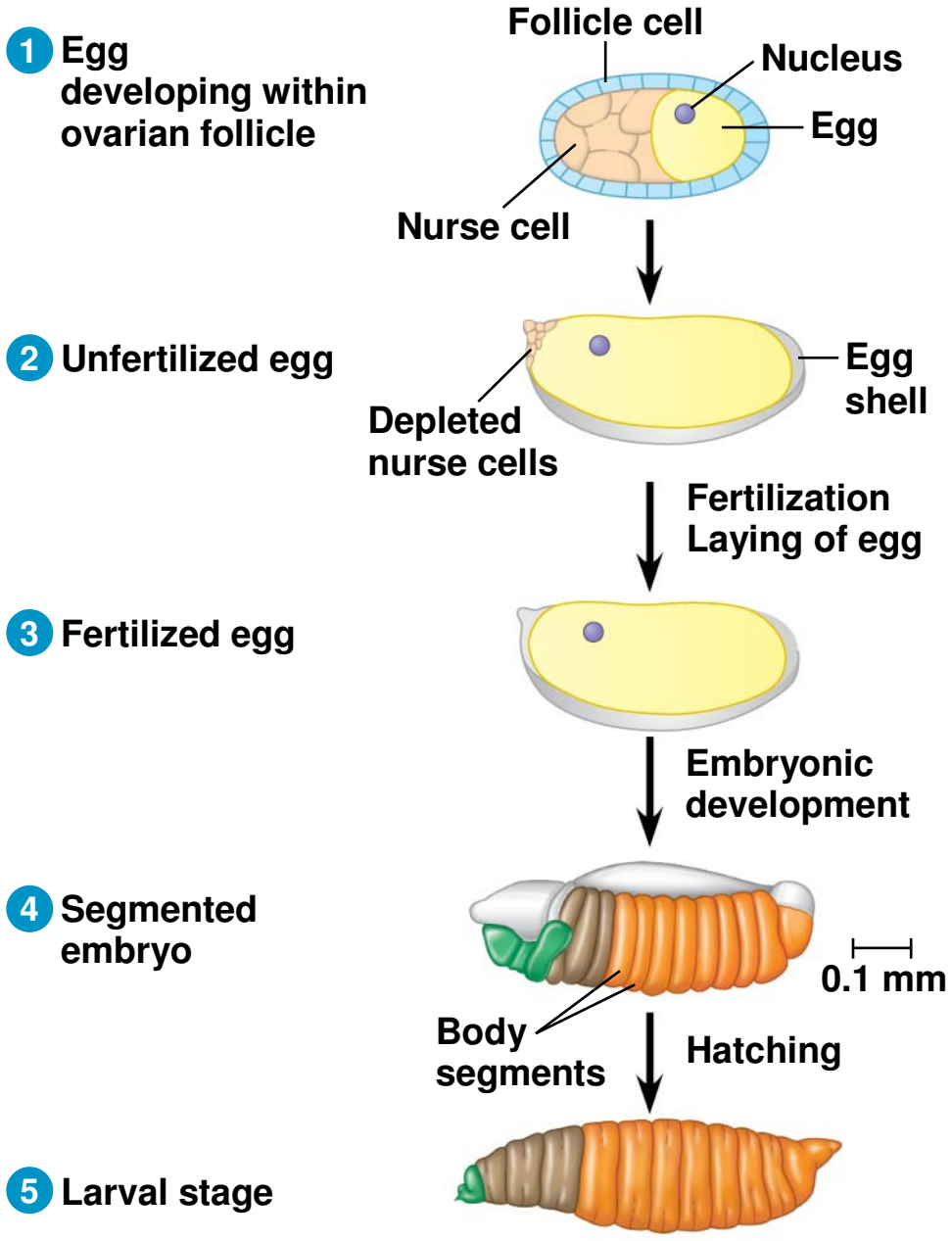
Pattern Formation: Setting Up the Body Plan

- **Pattern formation** is the development of a spatial organization of tissues and organs
  - In animals, pattern formation begins with the establishment of the major axes
- **Positional information** are the collective molecular cues that control pattern formation
  - Tells a cell its location relative to the body axes and to neighboring cells

Figure 16.7



(a) Adult

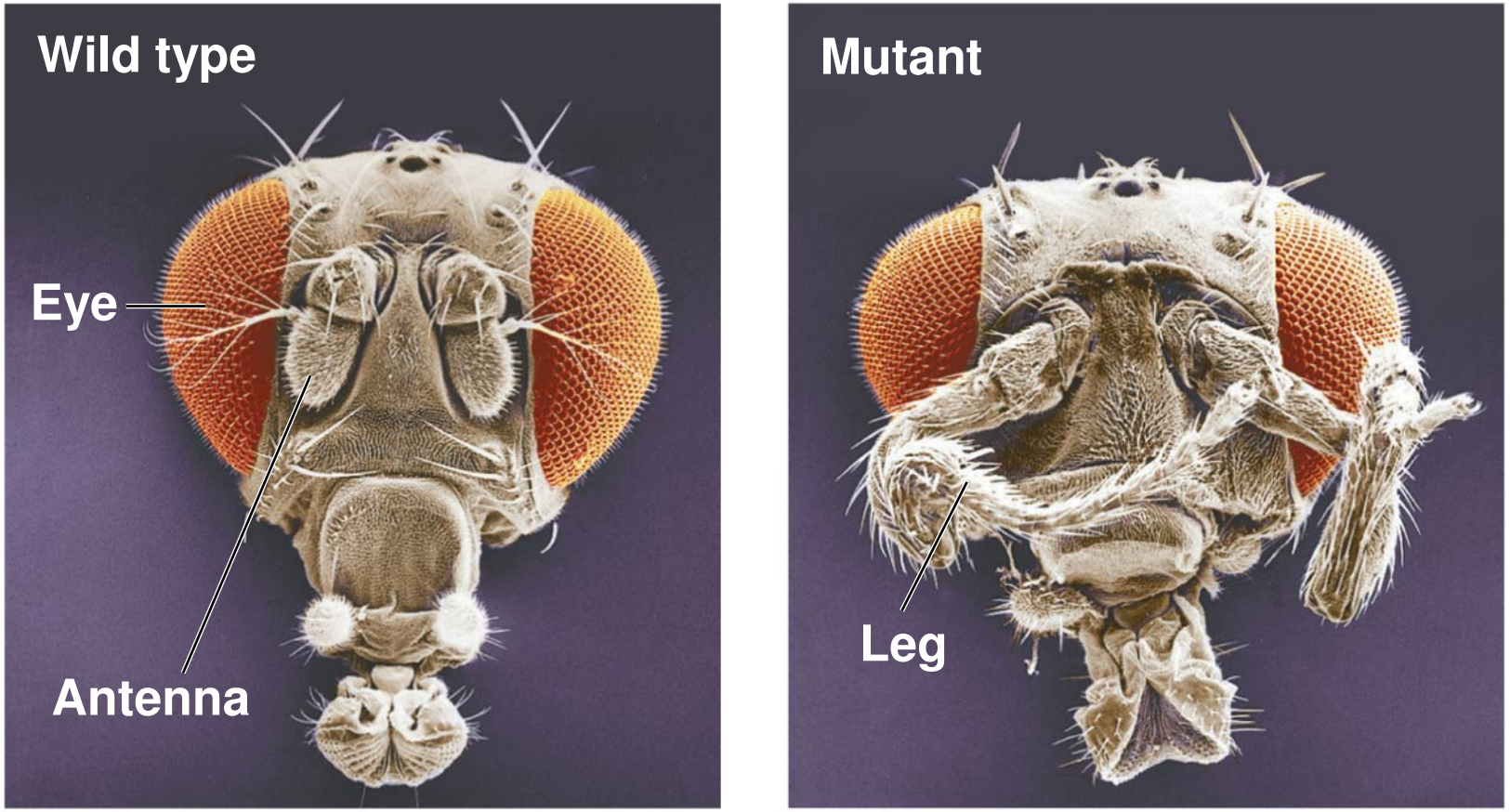


(b) Development from egg to larva

Genetic Analysis of Early Development: *Scientific Inquiry*

- Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus won a Nobel Prize in 1995 for decoding pattern formation in *Drosophila*
- Lewis connected developmental abnormalities to specific genes
- Studied bizarre mutant flies with developmental defects that led to extra wings or legs in the wrong place

Figure 16.8



- These regulatory genes are called **homeotic genes**
  - Control pattern formation in late embryo, larva, and adult stages
  - **Homeobox** =
    - 180-nucleotide sequence within homeotic and other developmental genes
- Homeotic genes in animals are named *Hox genes*
  - Highly conserved in all animals
- Different combinations of homeobox genes are active in different parts of an embryo
  - This selective expression of regulatory genes is central to pattern formation

- Hox genes regulate all of the transcription factors to turn on all of the genes required for a specific part of development
  - Hox genes are master regulatory genes
  - They control the transcription of transcription factors
    - Can turn genes on or off

- Nüsslein-Volhard and Wieschaus studied segment formation
  - They created mutants, conducted breeding experiments, and looked for the corresponding genes
- Many of the identified mutations were **embryonic lethals,** causing death during embryogenesis

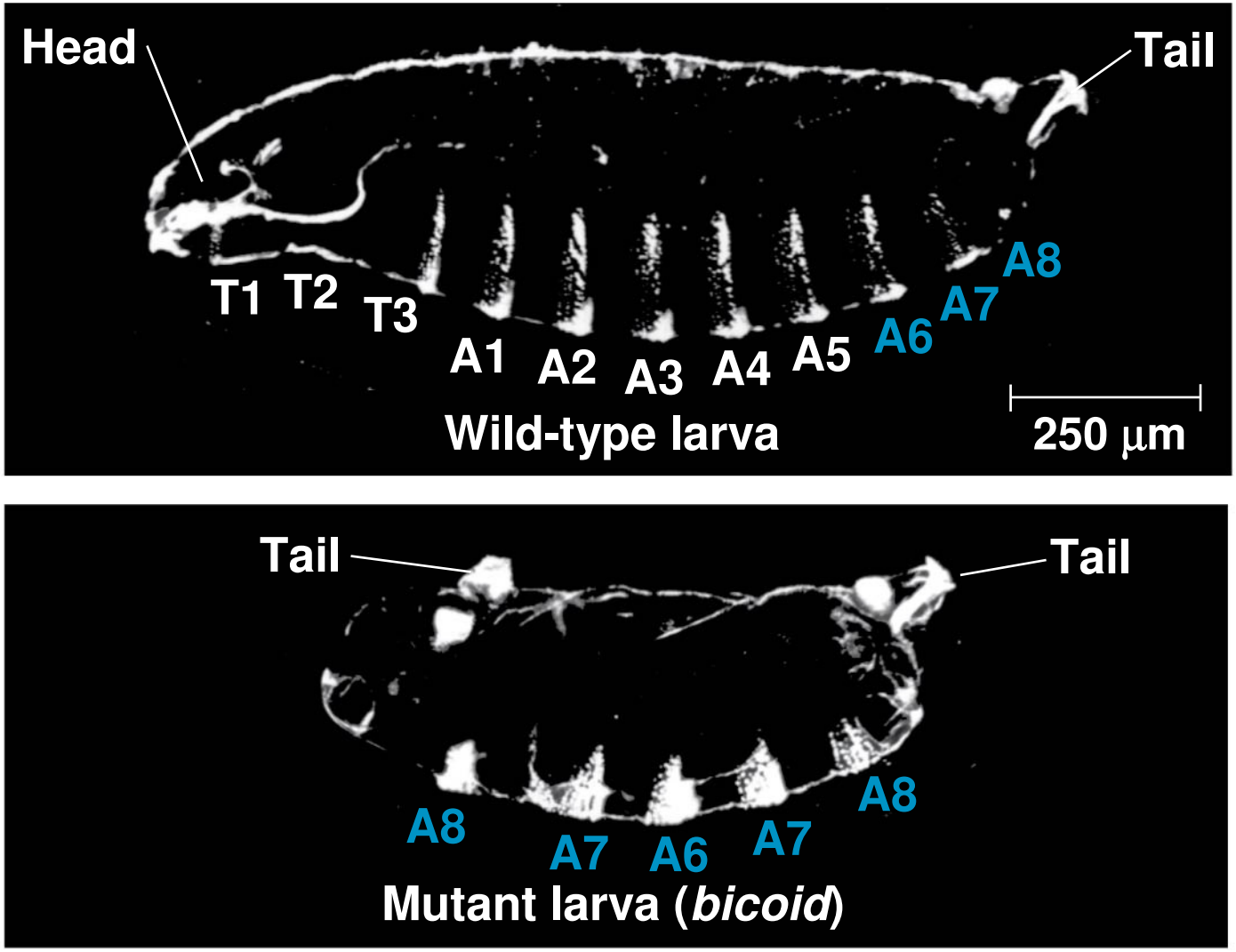
Axis Establishment

- **Maternal effect genes** encode cytoplasmic determinants that initially establish the axes of the body of *Drosophila*
- These maternal effect genes are also called **egg-polarity genes** because they control orientation of the egg and consequently the fly

Bicoid: A Morphogen Determining Head Structures

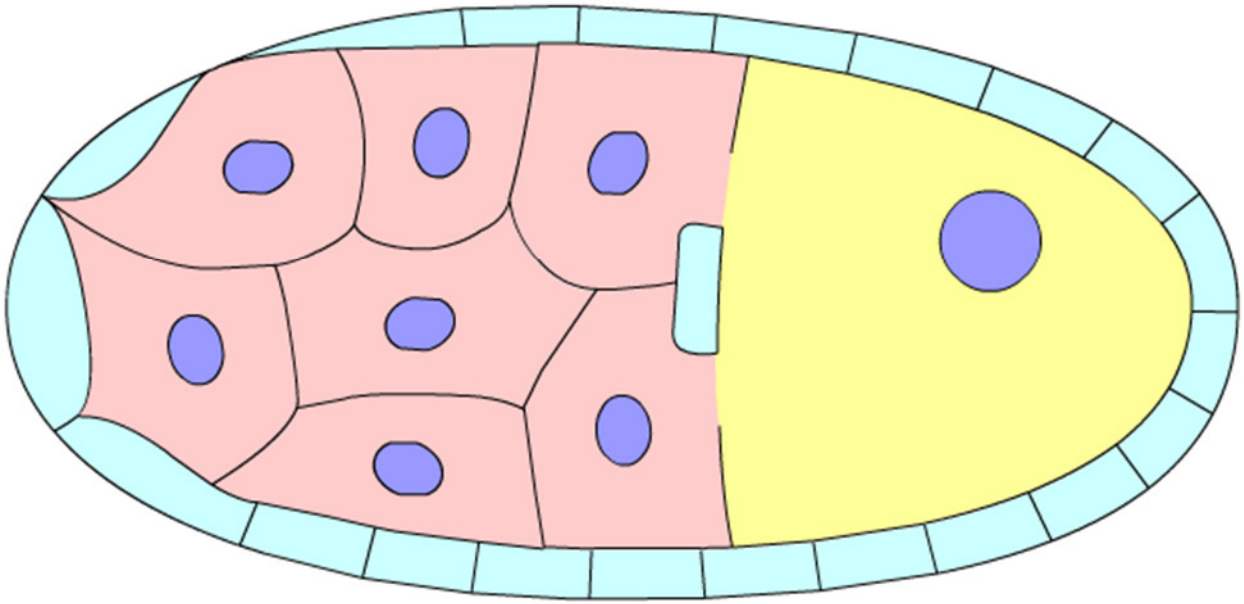
- One maternal effect gene, the ***bicoid*** gene, affects the front half of the body
- An embryo whose mother has no functional *bicoid* gene lacks the front half of its body and has duplicate posterior structures at both ends

Figure 16.9


Head
Tail
T1
T2
T3
A1
A2
A3
A4
A5
A6
A7
A8
Wild-type larva
250 μm
Tail
Tail
A8
A7
A6
A7
A8
Mutant larva (*bicoid*)

- This phenotype suggested that the product of the mother's *bicoid* gene is concentrated at the future anterior end
  - Thus is required for setting up the anterior end of the adult fly
- This hypothesis is an example of the morphogen gradient hypothesis
  - Gradients of substances called **morphogens** establish an embryo's axes and other features

- The *bicoid* mRNA is highly concentrated at the anterior end of the embryo
- After the egg is fertilized, the mRNA is translated into Bicoid protein, which diffuses from the anterior end
  - The result is a gradient of Bicoid protein
- Injection of *bicoid* mRNA into various regions of an embryo results in the formation of anterior structures at the site of injection



Animation: Head and Tail Axis of a Fruit Fly
Right click slide / Select play

Figure 16.10

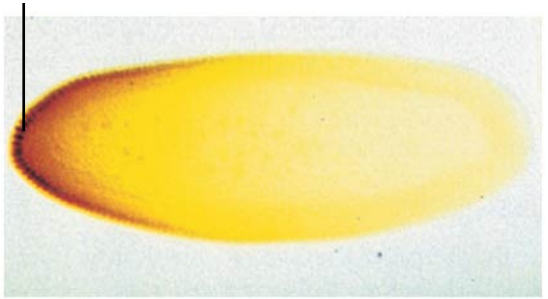
Results

Bicoid mRNA in mature unfertilized egg

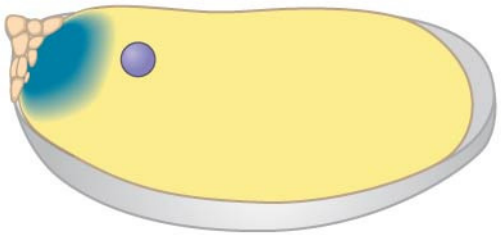
Fertilization, translation of *bicoid* mRNA

100 μm

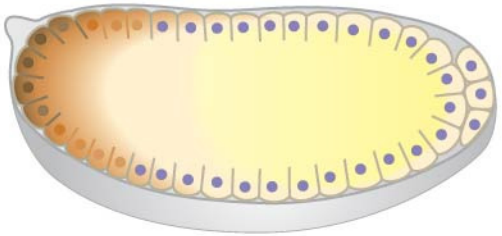
Anterior end



Bicoid protein in early embryo



Bicoid mRNA in mature unfertilized egg



Bicoid protein in early embryo

- The *bicoid* research is important for three reasons
  - It identified a specific protein required for some early steps in pattern formation
    - Helped us understand how different regions of the egg can give rise to cells that go down different developmental pathways
  - It increased understanding of the mother's critical role in embryo development
  - It demonstrated that a gradient of molecules can determine polarity and position in the embryo
    - A key developmental principle!

Concept 16.2: Cloning organisms showed that differentiated cells could be reprogrammed and ultimately led to the production of stem cells

- In organismal cloning one or more organisms develop from a single cell without meiosis or fertilization
- The cloned individuals are genetically identical to the "parent" that donated the single cell
- The current interest in organismal cloning arises mainly from its potential to generate stem cells

Cloning Plants and Animals

- F. C. Steward and his students first cloned whole carrot plants in the 1950s
- Single differentiated cells from the root incubated in culture medium were able to grow into complete adult plants
- This work showed that differentiation is not necessarily irreversible
- Cells that can give rise to all the specialized cell types in the organism are called **totipotent**

- In cloning of animals, the nucleus of an unfertilized egg cell or zygote is replaced with the nucleus of a differentiated cell, called *nuclear transplantation*
- The older the donor nucleus, the lower the percentage of normally development
  - Concluded that nuclear potential is restricted as development and differentiation proceeds

Reproductive Cloning of Mammals

- In 1997, Scottish researchers announced the birth of Dolly, a lamb cloned from an adult sheep by nuclear transplantation from a differentiated cell
- Dolly's premature death in 2003, and her arthritis, led to speculation that her cells were not as healthy as those of a normal sheep, possibly reflecting incomplete reprogramming of the original transplanted nucleus

Figure 16.12a

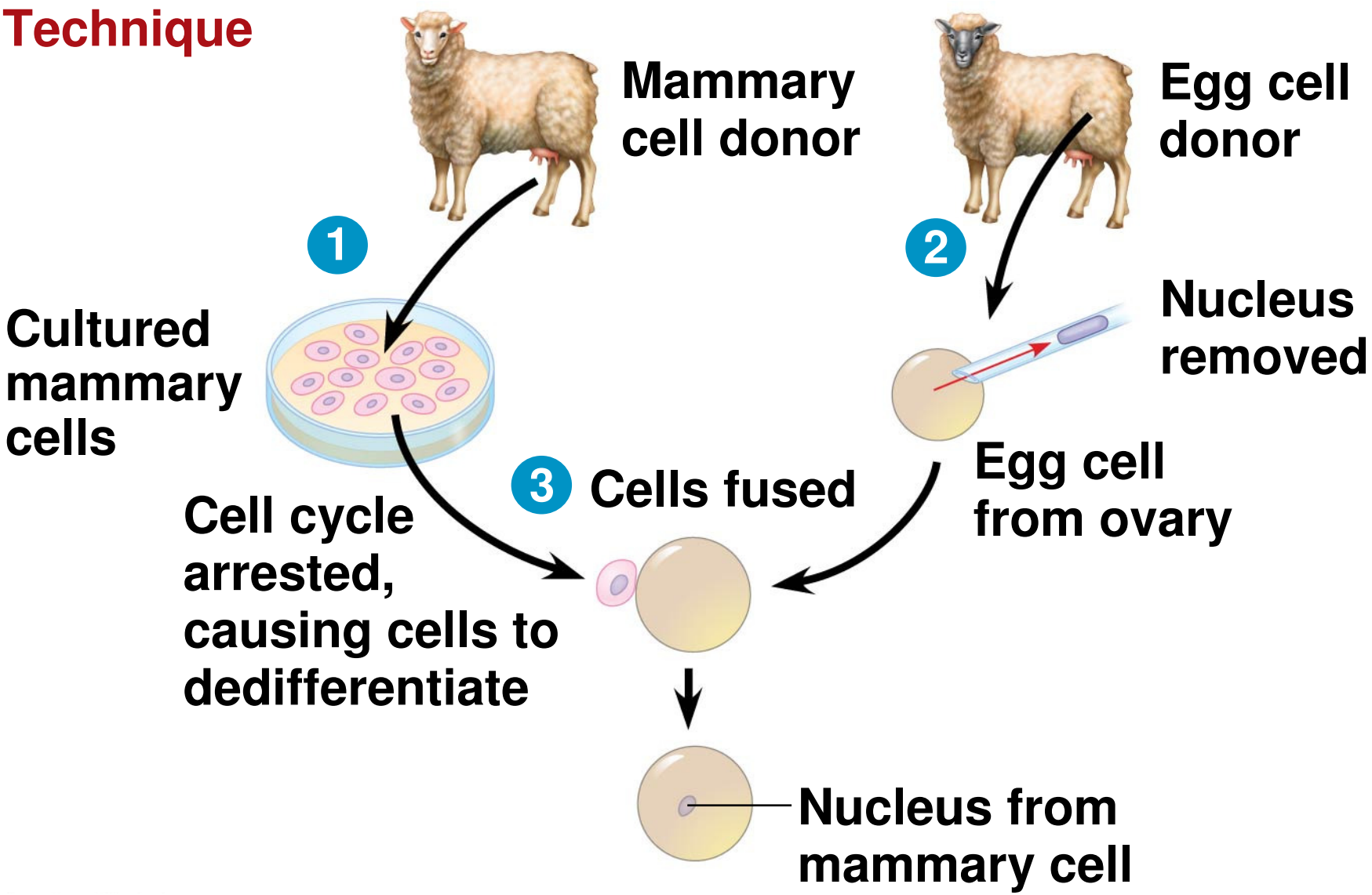
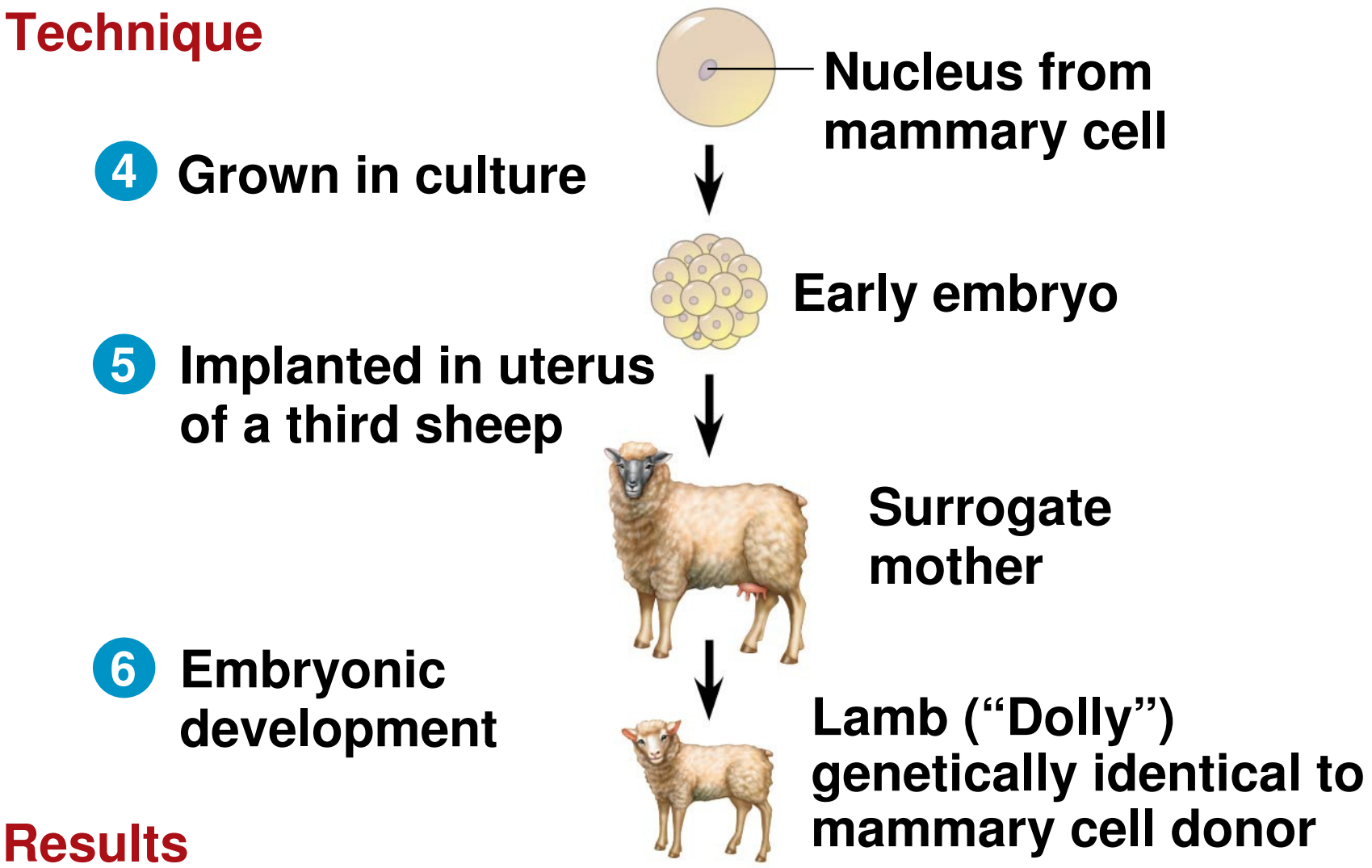
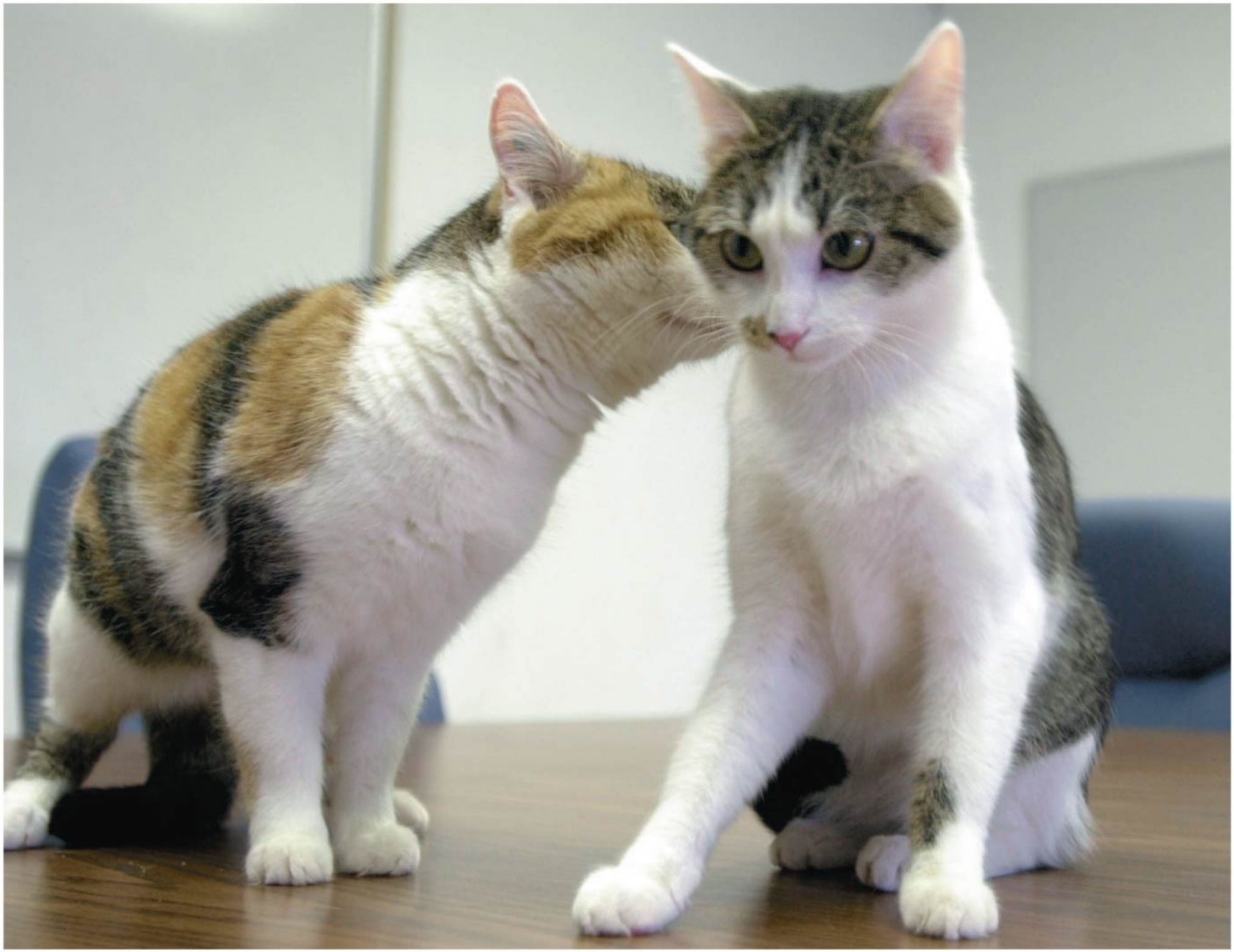


Figure 16.12b



- Since 1997, cloning has been demonstrated in many mammals, including mice, cats, cows, horses, mules, pigs, and dogs
  - When the goal is the production of new individuals, this is called *reproductive cloning*
- CC (for Carbon Copy) was the first cat cloned; however, CC differed somewhat from her female "parent"
  - Cloned animals do not always look or behave exactly the same as their "parent"
- Environmental influences and random phenomena can play a significant role during development

Figure 16.13



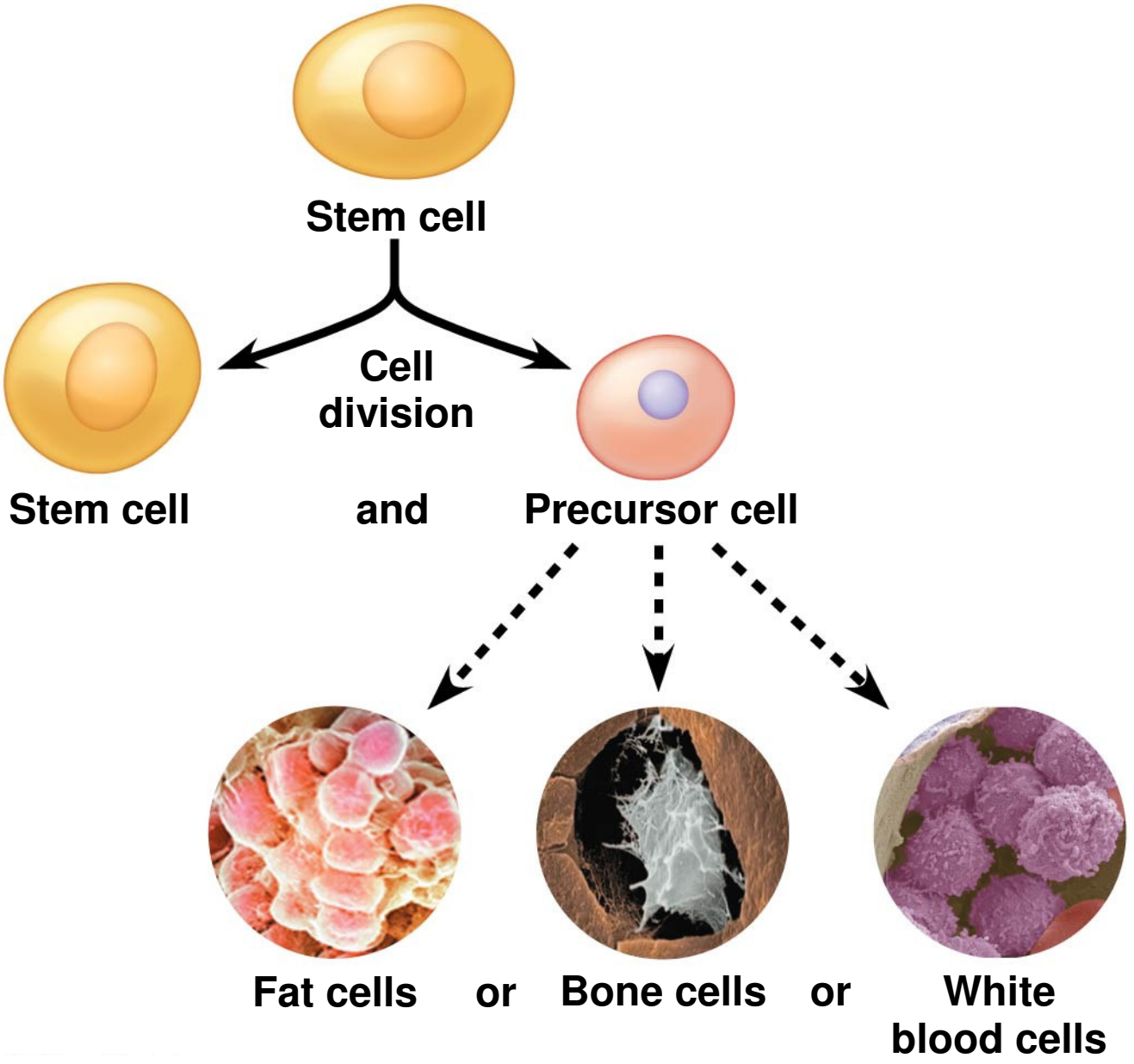
Faulty Gene Regulation in Cloned Animals

- In most nuclear transplantation studies, only a small percentage of cloned embryos have developed normally to birth
- Many cloned animals exhibit defects
  - IE-Low efficiency of cloning
  - High incidence of abnormalities

Stem Cells of Animals

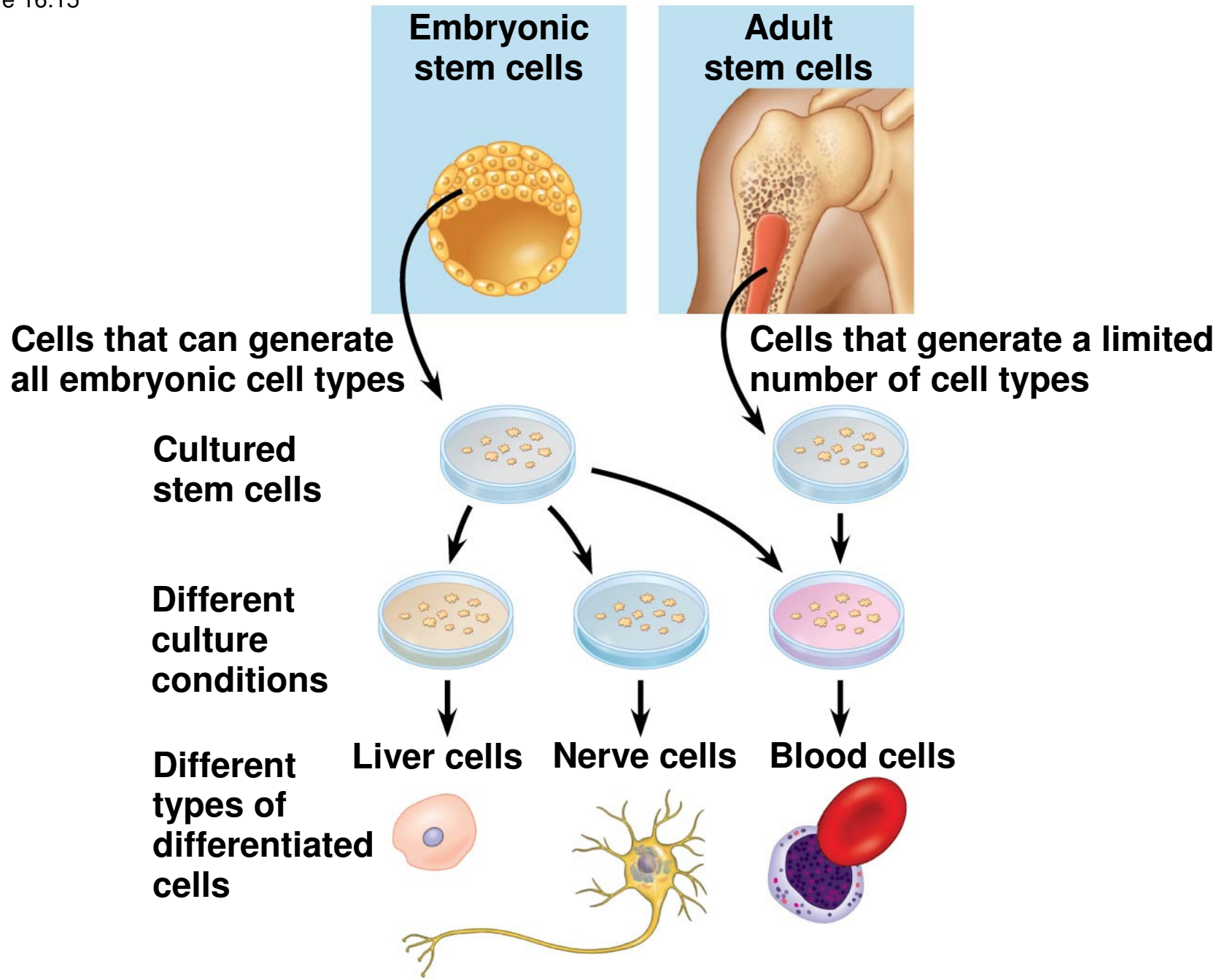
- A **stem cell** is a relatively unspecialized cell that can reproduce itself indefinitely and differentiate into specialized cells of one or more types
- Stem cells isolated from early embryos at the blastocyst stage are called *embryonic stem (ES) cells*
  - Reproduce indefinitely
  - **Pluriplotent**
    - Able to differentiate into many different cell types
  - Most versatile
  - Harvested from human embryos

Figure 16.14


Stem cell
Cell division
Stem cell
and
Precursor cell
Fat cells
or
Bone cells
or
White blood cells

- Researchers are able to reprogram fully differentiated cells to act like ES cells using retroviruses
  - Cells transformed this way are called *iPS,* or *induced pluripotent stem cells*
- The body also has *adult stem cells*, which replace nonreproducing specialized cells
  - Not able to give rise to all cell types in organism

Figure 16.15


Embryonic stem cells
Adult stem cells
Cells that can generate all embryonic cell types
Cells that generate a limited number of cell types
Cultured stem cells
Different culture conditions
Different types of differentiated cells
Liver cells
Nerve cells
Blood cells

- Ultimate aim of stem cell research is for medical applications
  - Supply cells for the repair of damaged or diseased organs
  - When the goal is to treat disease, this is called *therapeutic cloning*
- Cells of patients suffering from certain diseases can be reprogrammed into iPS cells
  - Study disease and test potential treatments
- In the field of regenerative medicine, a patient's own cells might be reprogrammed into iPS cells to potentially replace the nonfunctional (diseased) cells

Concept 16.3: Abnormal regulation of genes that affect the cell cycle can lead to cancer

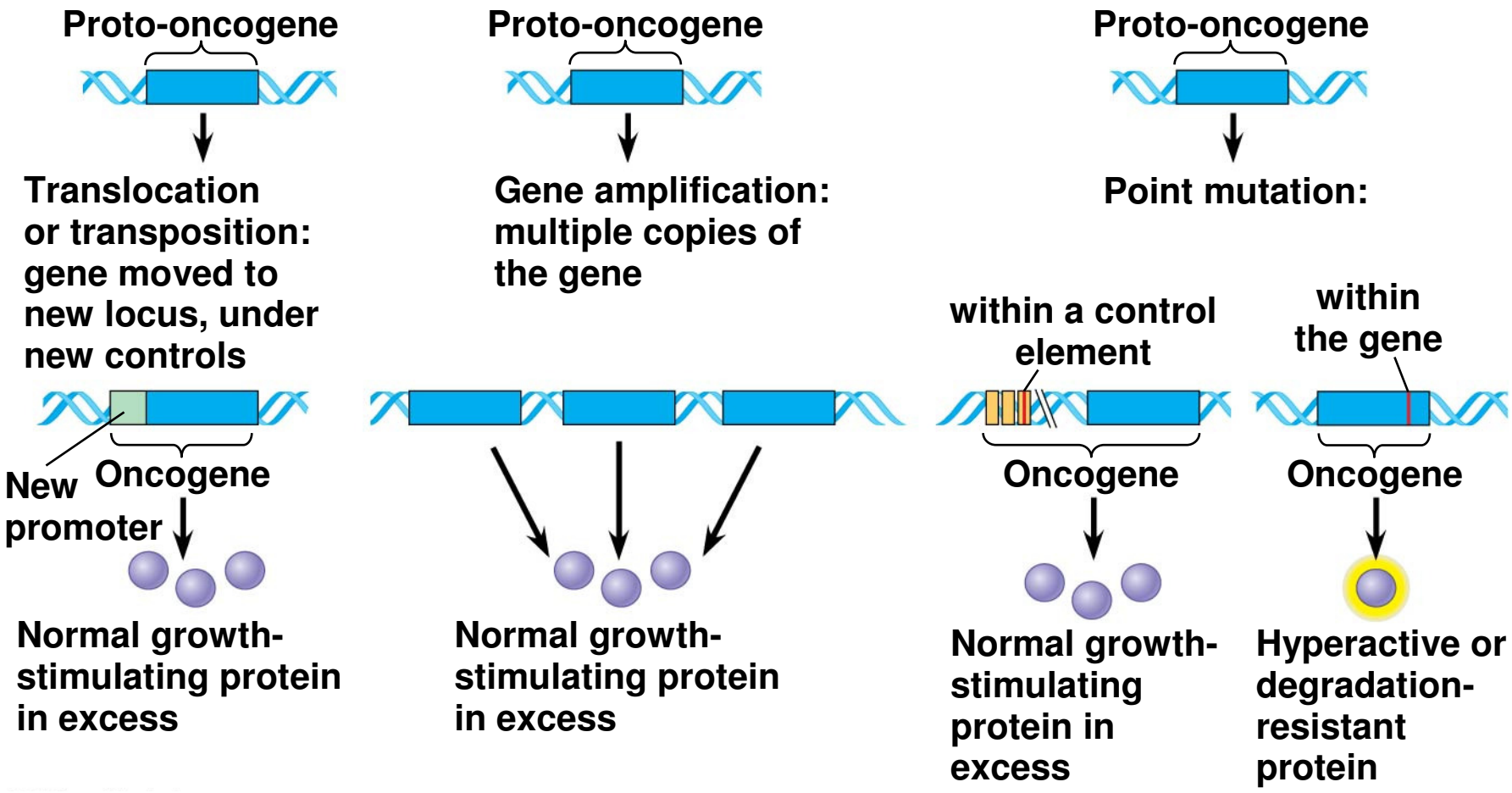
- The gene regulation systems that go wrong during cancer are the same systems involved in embryonic development
- Likely that many cancer-causing mutations result from environmental influences
  - Chemical carcinogens
  - Radiation
  - Some viruses

Types of Genes Associated with Cancer

- Cancer research led to the discovery of cancer-causing genes called **oncogenes** in certain types of viruses
- The normal version of such genes, called **proto-oncogenes**, code for proteins that stimulate normal cell growth and division
- An oncogene arises from a genetic change leading to either an increase in the amount or the activity of the protein product of the gene

- Proto-oncogenes can be converted to oncogenes by
  - Movement of the oncogene to a position near an active promoter, which may increase transcription
  - Amplification, increasing the number of copies of a proto-oncogene
  - Point mutations in the proto-oncogene or its control elements, causing an increase in gene expression

Figure 16.16


Proto-oncogene
Translocation or transposition: gene moved to new locus, under new controls
New promoter
Oncogene
Normal growth-stimulating protein in excess
Proto-oncogene
Gene amplification: multiple copies of the gene
Normal growth-stimulating protein in excess
Proto-oncogene
Point mutation:
within a control element
Oncogene
Normal growth-stimulating protein in excess
within the gene
Oncogene
Hyperactive or degradation-resistant protein

- Cancer cells are frequently found to contain chromosomes that have broken and rejoined incorrectly
  - Translocating fragments from one chromosome to another
- Result is abnormal stimulation of cell cycle
  - Puts cell on path to becoming malignant

- **Tumor-suppressor genes** encode proteins that help prevent uncontrolled cell growth
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
- Tumor-suppressor proteins
  - Repair damaged DNA
  - Control cell adhesion
  - Inhibit the cell cycle

The Multistep Model of Cancer Development

- Multiple somatic mutations are generally needed for full-fledged cancer
  - Thus the incidence increases with age
- About half a dozen changes must occur at the DNA level for a cell to become fully cancerous
- These changes generally include at least one active oncogene and the mutation or loss of several tumor-suppressor genes

Inherited Predisposition and Other Factors Contributing to Cancer

- Individuals can inherit oncogenes or mutant alleles of tumor-suppressor genes
- Mutations in the *BRCA1* or *BRCA2* gene are found in at least half of inherited breast cancers
  - Tests using DNA sequencing can detect these mutations

- DNA breakage can contribute to cancer
- The risk of cancer can be lowered by minimizing exposure to agents that damage DNA
  - IE-ultraviolet radiation and chemicals found in cigarette smoke
- Also, viruses play a role in about 15% of human cancers by donating an oncogene to a cell, disrupting a tumor-suppressor gene, or converting a proto-oncogene into an oncogene
  - Examples: Epstein-Barr virus, Papillomavirus